

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 233/30, 233/32, 233/36, 233/70, 235/00, 235/02</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/38847</b> <b>(43) International Publication Date:</b> 5 August 1999 (05.08.99)
<b>(21) International Application Number:</b> PCT/US99/01201 <b>(22) International Filing Date:</b> 20 January 1999 (20.01.99) <b>(30) Priority Data:</b> 60/073,103 30 January 1998 (30.01.98) US <b>(71) Applicant:</b> BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). <b>(72) Inventors:</b> ANDERSON, Neal, G.; 129 Upper Creek Road, Stockton, NJ 08559 (US). DESHPANDE, Rajendra.; 47 Longfield Drive, Neshanic Station, NJ 08853 (US). MO-NIOT, Jerome, L.; 139 South Road, Chester, NJ 07930 (US). <b>(74) Agents:</b> ALMAULA, Prabodh, I. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> METHOD FOR PREPARING N-SUBSTITUTED HETEROCYCLIC DERIVATIVES USING A PHASE-TRANSFER CATALYST  <b>(57) Abstract</b>  Disclosed is a process for preparing N-substituted heterocyclic derivatives and its salts using phase transfer catalysis.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

METHOD FOR PREPARING N-SUBSTITUTED HETEROCYCLIC  
DERIVATIVES USING A PHASE-TRANSFER CATALYST

5

Background of the Invention

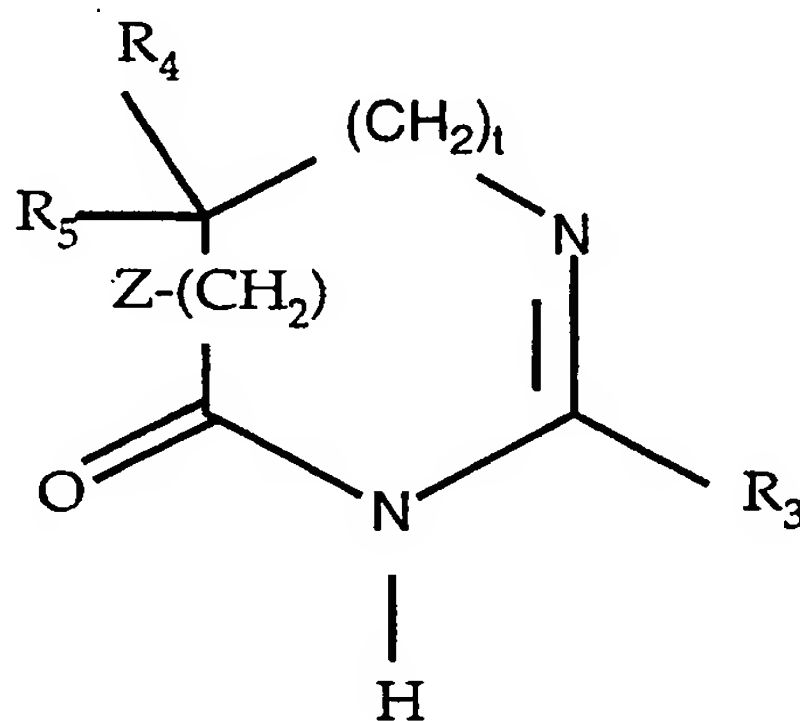
The present invention is directed to a process for preparing N-  
10 substituted heterocyclic derivatives 4'-[[2-alkyl or alkoxy-4-oxo-1,3-  
diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile and its  
salts using phase transfer catalysis. These compounds are important  
intermediates in the synthesis of the final compounds 2-alkyl or alkoxy-  
3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1,3-diazaspiro[4.4]non-  
15 1-en-4-one and its salts which are useful as antagonists of the peptide  
hormone Angiotensin II.

Angiotensin II is a peptide hormone of the formula H-Asp-Arg-  
Val-Tyr-Ile-His-Pro-Phe-OH.

Angiotensin II is a potent vasopressor and the biologically active  
20 product of the renin-angiotensin system. Renin acts on the  
angiotensinogen of the plasma to produce angiotensin I, which is  
converted to angiotensin II by the action of the angiotensin I converting  
enzyme. The final compounds inhibit the action of angiotensin II on its  
receptors and thus prevents the increase in blood pressure produced by  
25 the hormone-receptor interaction. Thus, they are therefore useful in the  
treatment of hypertension and heart failure.

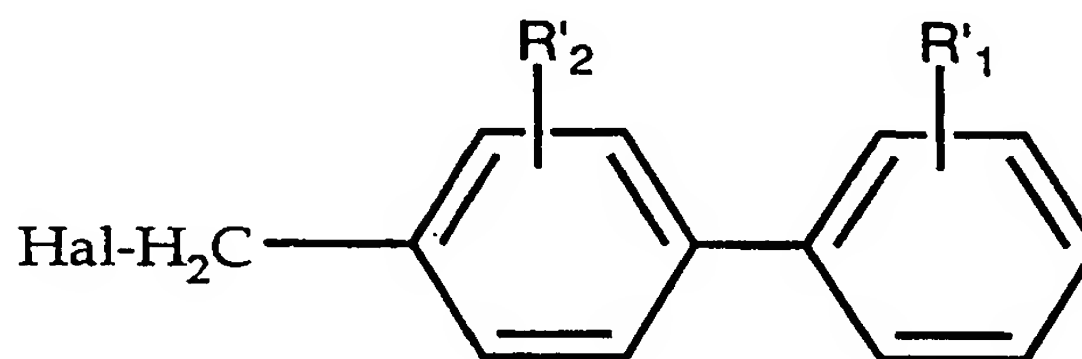
The preferred intermediate is 4'-[[2-butyl-4-oxo-1,3-  
diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile which  
is useful in the synthesis of the final compound 2-butyl-3-[[2'-(1H-  
30 tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-  
one known by the trademark (Irbesartan) and can be easily converted to  
Irbesartan and its salts according to the process described in U. S.  
Patent No. 5,270,317. The compound Irbesartan antagonizes the action  
of angiotensin II.

A synthetic route for the preparation of N-substituted heterocyclic derivatives has been described in U.S. Patent No. 5,270,317. The process of U.S. Patent No. 5,270,317 involves reacting a heterocyclic compound of the formula



5

with a (biphenyl-4-yl)methyl derivative of the formula



10

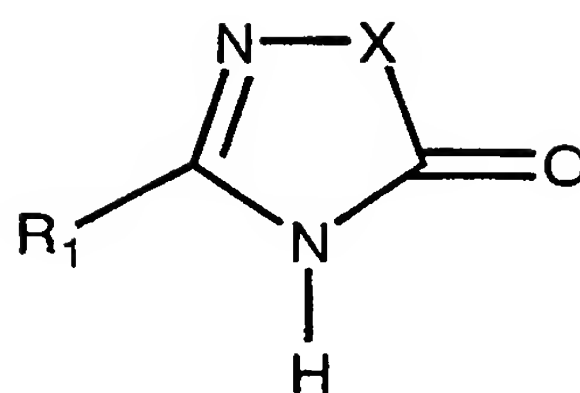
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $t$ ,  $z$  and Hal have the meanings given in said U.S. Patent No. 5,270,317, in the presence of an inert solvent such as DMF, DMSO or THF, with a basic reagent, for example KOH, a metal alcoholate, a metal hydride, calcium carbonate or triethylamine. The products of the reaction were purified by chromatography.

15

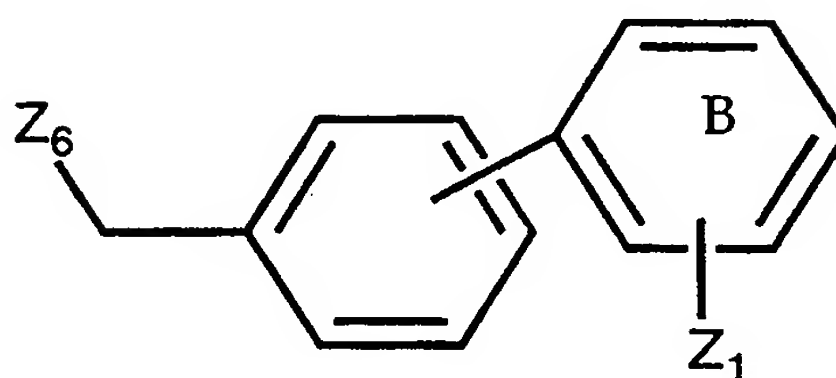
U. S. Patent Nos. 5,352,788, and 5,559,233, and WO 91/14679 also describe identical alkylation of the nitrogen atom of the heterocyclic compound with the halo-biphenyl compound using the same inert solvent and the same basic reagents.

20

Also EP0 475,898 describes the alkylation of the nitrogen atom of the heterocycle of the formula



with a compound of the formula



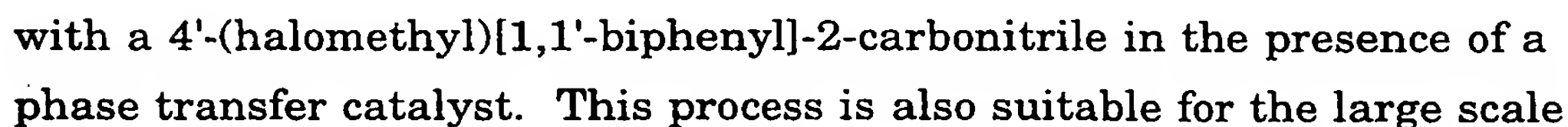
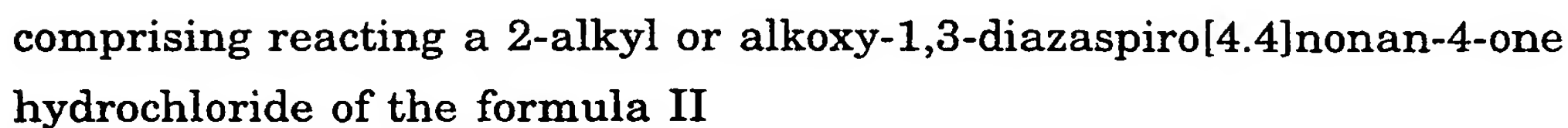
wherein X, R<sub>1</sub>, Z<sub>1</sub> and Z<sub>6</sub> have the meanings given therein, in the presence of N, N-dimethylformamide and a basic reagent, such as alkalimetalhydrides for example sodium or potassium hydride.

10 All of the above identified patents describe alkylation in solvents, such as N,N-dimethylformamide or DMSO, etc. in the presence of a basic reagent, for example, a metal hydride or a metal alcoholate etc. The strong bases, such as metal hydride or a metal alcoholate require anhydrous reaction conditions. Since N,N-dimethylformamide is used  
15 as a solvent, its removal requires high temperature concentration by distillation, which can result in degradation of the final product. None of these patents describe alkylation using a phase transfer catalysis.

The Journal of Heterocyclic chemistry, 21 477-480, 1984 describes alkylation of hydantoins using a phase-transfer catalysis. The  
20 hydantoins are by their electronic nature more acidic than the 2-butyl-1,3-diazaspiro[4.4]nonan-4-one, hydrochloride of the present invention and therefore, there is structural divergence between the two compounds.

The object of the present invention is the provision of a process for the preparation of N-substituted heterocyclic derivative 4'-[[2-alkyl or alkoxy-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile and its salts using a phase transfer catalyst.

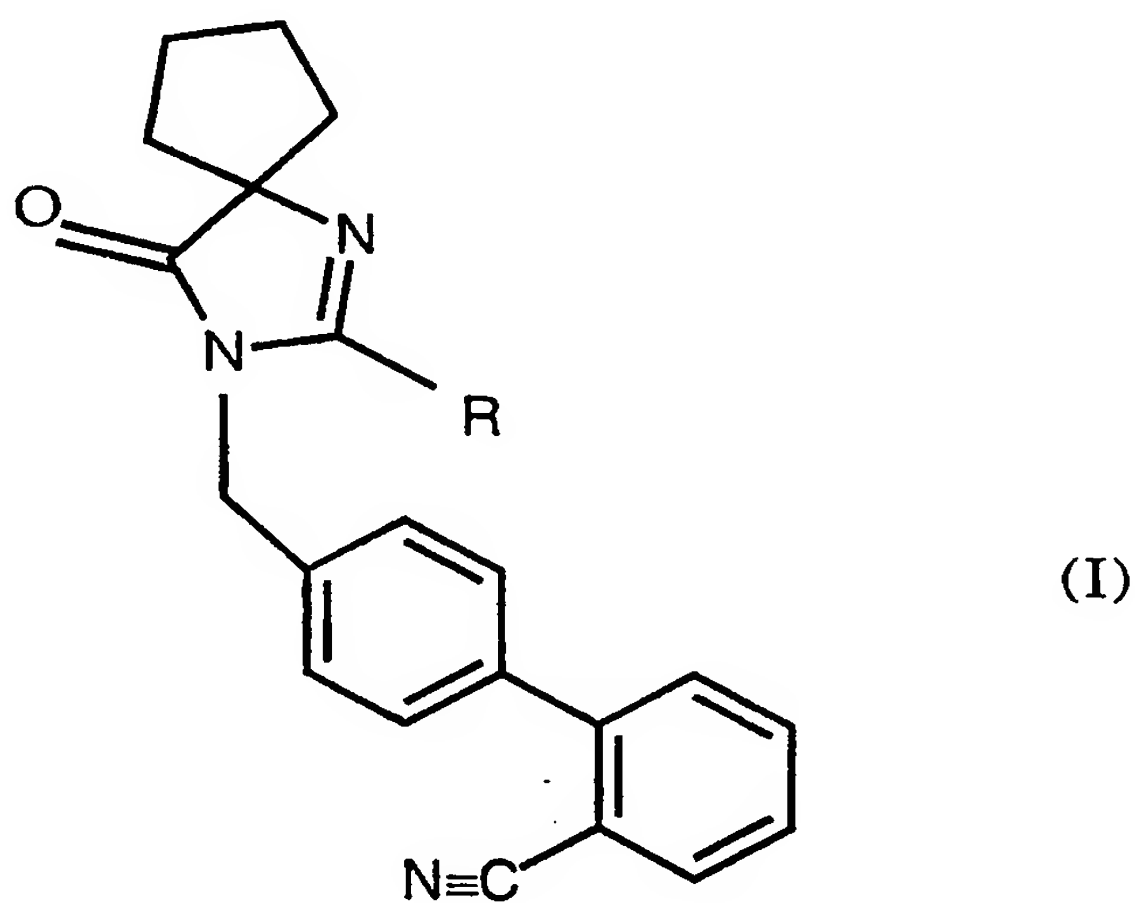
10



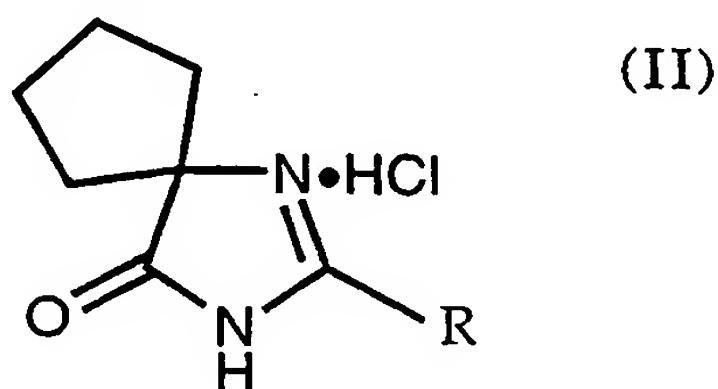
preparation of the intermediate of formula I. The substituent R is lower alkyl or lower alkoxy and the halogen is chlorine, bromine or iodine.

### Detailed Description

5       The present invention is directed to a process for preparing a 4'-[[2-alkyl or alkoxy-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile and its salts, an intermediate having the following structural formula I:

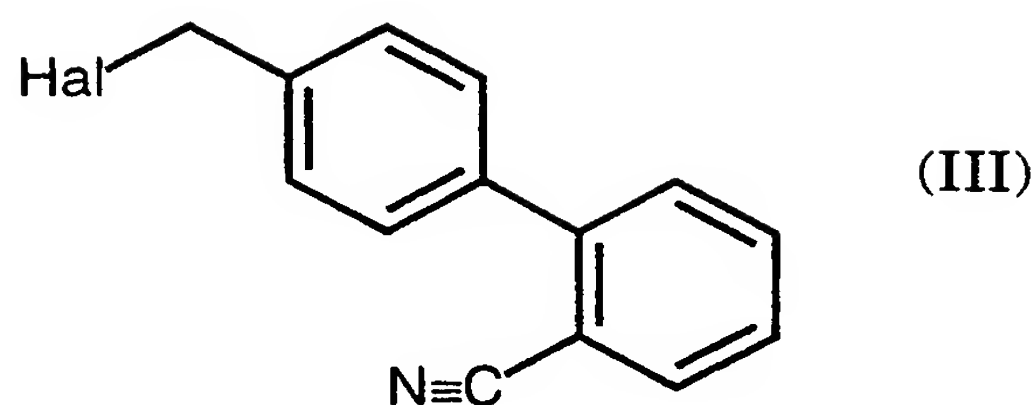


10       comprising reacting a 2-R-1,3-diazaspiro[4.4]nonan-4-one hydrochloride of the formula II



15       with a 4'-(halomethyl)[1,1'-biphenyl]-2-carbonitrile of the formula III





in the presence of a phase-transfer catalyst. The substituent R is lower alkyl of 1-4 carbon atoms or lower alkoxy of 1-3 carbon atoms. The lower  
5 alkyl of 1-4 carbon atoms is methyl, ethyl, n-propyl or n-butyl. The lower alkoxy of 1-3 carbon atoms is methoxy, ethoxy or n-propoxy. The preferred lower alkyl is n-butyl and the preferred lower alkoxy is n-propoxy. The hal is chlorine, bromine or iodine. The preferred halogen atom is bromine. The salts of the compound of formula I or Irbesartan  
10 are pharmaceutically acceptable salts such as the hydrochloride, the hydrobromide, the sulfate or the hydrogen sulfate.

Thus, in accordance with the process of the present invention, the alkylation of the nitrogen atom at the 1-position of the 2-R-1,3-diazaspiro[4.4]nonan-4-one hydrochloride is carried out using phase-  
15 transfer catalysis. Under the conditions of the phase-transfer catalysis, the substrates 2-R-1,3-diazaspiro[4.4]nonan-4-one hydrochloride of the formula II and 4'-(halomethyl)[1,1'-biphenyl]-2-carbonitrile of formula III are allowed to react, with vigorous stirring in a volatile, water-immiscible organic solvent in the presence of a catalytic amount of a  
20 phase transfer agent and an aqueous solution of standard inorganic bases. The reaction proceeds at ambient temperature and pressure for two to three hours. After that the reaction mixture is diluted with water, if initially less water is present or when more water is present initially, then it is not necessary to dilute the reaction mixture with water. The  
25 two phases, that is organic and aqueous, are separated and the organic phase is washed twice with water. Then the organic phase is optionally dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure to an oily residue. The oily residue is crystallized from an organic solvent to give the final product. The final product can be  
30 converted into its salt by methods known in the prior art.

The organic solvent can be any water-immiscible solvent, for example, dichloromethane or toluene and the standard inorganic bases can be aqueous sodium hydroxide or potassium hydroxide. The phase-transfer catalyst is, for example, methyl tributylammonium chloride but  
5 can be any phase-transfer catalyst. The crystallization solvent can be any organic solvent that helps crystallization, such as methyl-tert-butyl-ether.

The starting materials are readily available or can be prepared by methods known in the literature including the aforementioned patents.

10 A preferred embodiment of the process comprises reacting a 2-butyl-1,3-diazaspiro[4.4]nonan-4-one hydrochloride and 4'-(bromomethyl)[1,1'-biphenyl]-2-carbonitrile in a water-immiscible organic solvent such as dichloromethane or toluene, in the presence of methyl-tributylammonium chloride and aqueous sodium or potassium  
15 hydroxide, separating the organic phase of dichloromethane or toluene, washing the separated organic phase with water, optionally drying the organic phase over a desiccant, filtering the organic phase, evaporating the organic phase to an oily residue and finally crystallizing the oily residue from an organic solvent, such as methyl tert. butyl ether to give  
20 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl]methyl][1,1'-biphenyl]-2-carbonitrile. This compound is an intermediate in the synthesis of the compound 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one known by the trademark (Irbesartan) and can be easily converted to Irbesartan and its salts according to the  
25 process described in U. S. Patent No. 5,270,317. The compound Irbesartan antagonizes the action of angiotensin II.

Thus, N-alkylation by phase-transfer catalysis according to the present process provides conditions that are superior and advantageous than those described in the prior art for N-alkylation without the phase-  
30 transfer catalysis. In the present process, there is no need for chromatography and the final product is readily isolated by crystallization. Moreover, no special handling details are required in the present process, since no sodium hydride or sodium or potassium methoxide is used. In addition the reaction time in the present process

is of short duration and consequently results in increased productivity.  
The following examples illustrate the invention.

### Example 1

5        Preparation of 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl]methyl][1,1'-biphenyl]-2-carbonitrile

Alkylation in toluene - 50% NaOH.

A mixture of 0.231 g (1.0 mmol) of 2-butyl-1,3-diazaspiro[4.4]nonan-4-one, hydrochloride, 0.272 g (1.0 mmol) of 4'-(bromomethyl)[1,1'-biphenyl]-2-carbonitrile, 24.4 µL (0.075 mmol) of 75%  
10        aqueous solution of methyl-tributylammonium chloride, 2.0 mL of toluene and 2.0 mL of 50% aqueous solution of sodium hydroxide was vigorously stirred at room temperature for 2.2 hours. Then the reaction mixture was diluted with 2 mL of water and the two phases separated.  
15        The organic phase was extracted twice with 2 mL of water, evaporated under vacuum to give 0.33 g (85.7%) of the title compound.

1H-NMR:    d (delta) 7.8 - 7.2 (m, 8H); 4.8 (s, 2H); 2.4 (m, 2H);  
              2.0 (m, 8H); 1.6 (m, 2H); 1.35 (m, 2H); 0.9 (t, 3H).

20

13C-NMR:    d (delta) 186.7, 161.4, 144.6, 137.5, 137.1, 132.8, 129.9, 129.3  
              128.9, 128.1, 127.7, 127.0, 125.1, 118.5, 111.0, 76.5, 43.2, 37.3,  
              28.7, 27.7, 26.0, 22.2, 13.6.

25

### Example 2

Preparation of 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl]methyl][1,1'-biphenyl]-2-carbonitrile

Alkylation in Dichloromethane - 33% NaOH

A mixture of 37 g, (160 mmoles) of 2-butyl-1,3-diazaspiro[4.4]nonan-4-one, hydrochloride, 1.7 mL of a 75% aqueous  
30        solution of methyl tributylammonium chloride, 125 mL of a 33% (10 N) aqueous solution of sodium hydroxide and 125 mL of methylene chloride was vigorously stirred at room temperature for five minutes. To this vigorously stirred mixture was added a solution of 44.34 g (163.6 mmoles

as determined quantitatively by HPLC) of 4'-(bromomethyl)[1,1'-biphenyl]-2-carbonitrile in 400 mL of methylene chloride over a period of 40 to 60 minutes. After that, the phases were separated and the organic phase was washed twice with 100 mL of water. Then the organic phase was evaporated under reduced pressure to give an oily residue. The oily residue was dissolved in 250 mL of methyl-tertiarybutyl ether and the resulting solution was treated with 110 mL of concentrated HCl at a temperature below 40°C. Then the biphasic mixture was stirred for 10 minutes, allowed to settle and the phases separated. The aqueous acidic phase was washed once with 150 mL of methyl-tertiarybutyl ether. Then the aqueous acidic phase was divided into two equal portions and one portion was used for crystallization. To one stirred portion were added 25 mL of DMF and 25 mL of methyl-tertiarybutyl ether and 55 mL of 33% aqueous sodium hydroxide over a period of two to three hours. The slurry was allowed to stir overnight and then a total of 50 mL of water was added to the slurry and the slurry additionally stirred for 45 minutes. After that the slurry was cooled to 0° in an ice bath for 35 minutes and filtered. The wet cake remaining on the filter paper was washed once with a mixture of 90 mL/10 mL of water and methyl-tertiarybutyl ether. Then the cake was dried in a vacuum oven at 40°C and at pressure of 2.3 mm Hg to give 23.3 g (yield 75.4%) of the title compound having a laboratory HPLC of HI of 99.8.

### Example 3

#### Preparation of 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl]methyl][1,1'-biphenyl]-2-carbonitrile

Alkylation in Dichloromethane - 33% NaOH

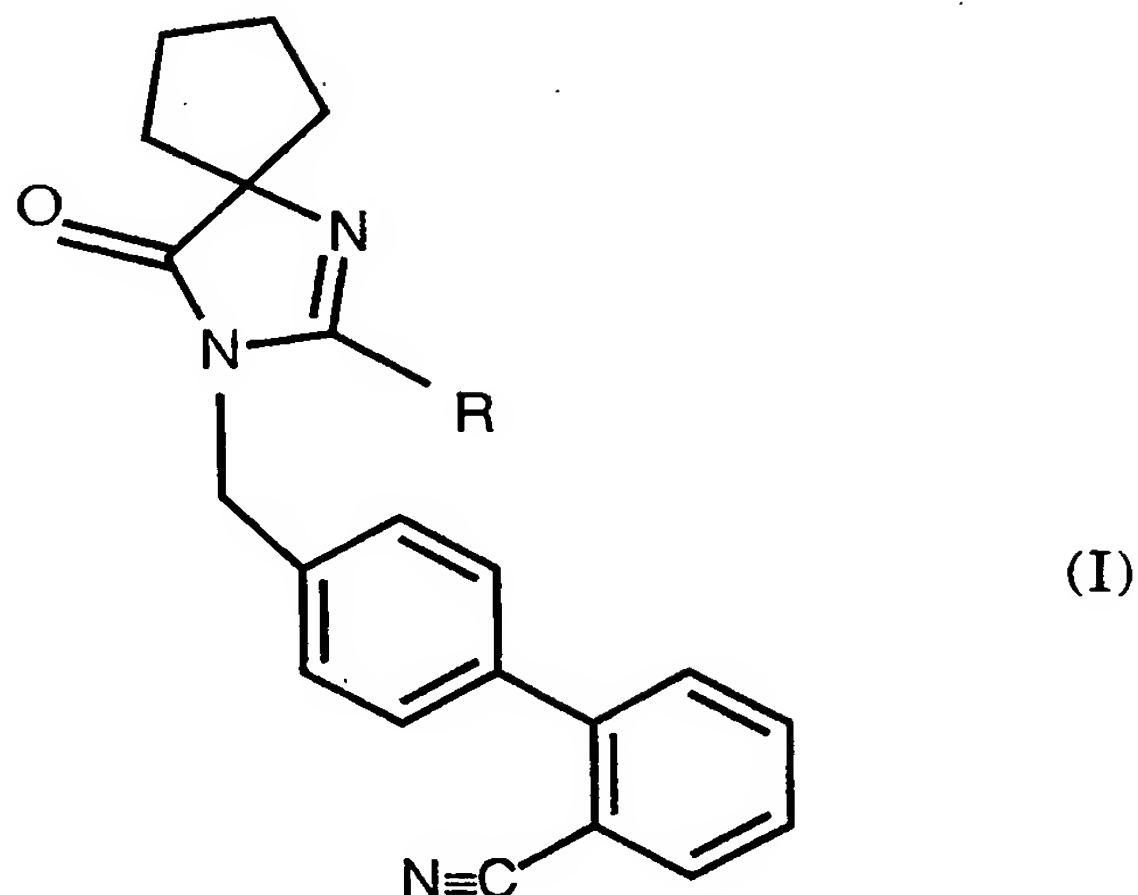
A mixture of 28.9 g (125 mmoles) of 2-butyl-1,3-diazaspiro[4.4]nonan-4-one, hydrochloride, 1.3 mL of 75% aqueous solution of methyl tributylammonium chloride, 90 mL (10 N) of 33% aqueous sodium hydroxide and 90 mL of methylene chloride was vigorously stirred for 5 minutes at room temperature and then cooled to 7-12°C. To this vigorously stirred cooled mixture at 7-12°C was added a solution of 36.04 g (132 mmoles, amount determined quantitatively by

HPLC) in 300 mL of methylene chloride of 4'-(bromomethyl)[1,1'-biphenyl]-2-carbonitrile over a period of 70 minutes. After that, the reaction mixture was allowed to warm up to room temperature and stirred additionally at room temperature for a half hour. Then the  
5 phases were separated and the organic phase was washed twice with 90 mL of water. The organic phase was concentrated under reduced pressure to the minimum agitation volume, and methyl tertiarybutyl ether was added. Concentration was continued to displace the dichloromethane, and the product was crystallized from the methyl  
10 tertiarybutyl ether solution. The crystals were collected on a filter, washed with cold 120 ml of methyl-tertiarybutyl ether and dried in a vacuum oven at 40°C and a pressure of 3.1 mm Hg to give 39.9 g (82.4%) of the title compound having a laboratory HPLC of HI 99.8.

What is claimed is:

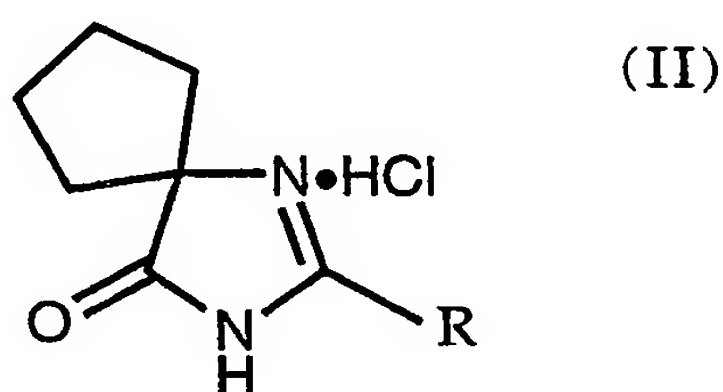
1. A process for the preparation of a compound of formula I or its salt

5

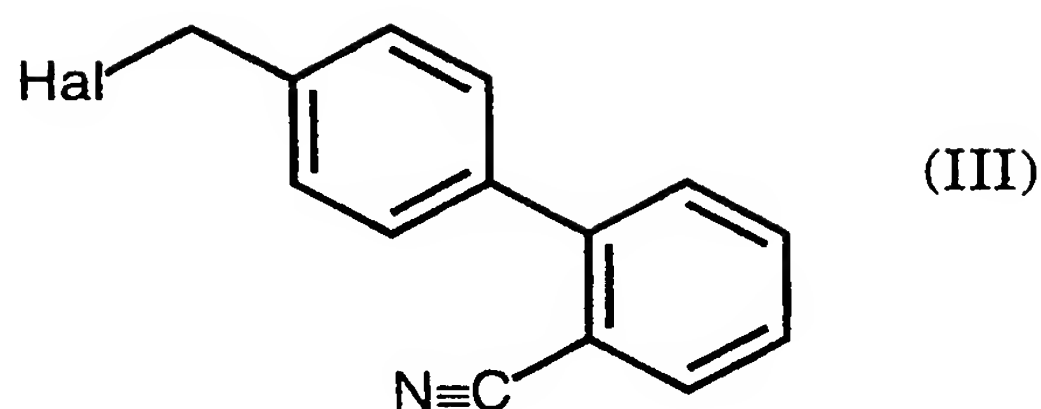


wherein R is lower alkyl of 1-4 carbon atoms or lower alkoxy of 1-3 carbon atoms, comprising the steps of :

- 10 reacting a 2-R-1,3-diazaspiro[4.4]nonan-4-one hydrochloride of formula II



- 15 wherein R has the meaning given above, with a 4' (halomethyl)[1,1'-biphenyl]-2-carbonitrile of a formula III



wherein Hal is chlorine, bromine or iodine, in a water-immiscible organic solvent, in the presence of an inorganic base and a phase transfer catalyst, separating the organic solvent, drying the organic solvent, filtering the organic solvent, evaporating the filtered organic solvent to give the compound of the formula I, crystallizing the compound of the formula I from an organic solvent and optionally converting the compound of formula I into its salt.

10

2. The process of claim 1, wherein R is methyl, ethyl, n-propyl, n-butyl, methoxy, ethoxy or propoxy and hal is bromine.

3. The process of claim 1, wherein R is n-butyl or propoxy and hal is bromine.

15

4. The process of claim 1, wherein the water-immiscible organic solvent is methylene chloride or toluene and the inorganic base is sodium hydroxide or potassium hydroxide.

20

5. The process of claim 1, wherein the phase-transfer catalyst is methyl tributylammonium chloride.

6. The process of claim 1, wherein the reaction is carried out at room temperature.

25

7. The process of claim 1 wherein the compound of formula I is crystallized from methyl-tertiarybutyl ether.



8. The process of claim 1, wherein the salt is hydrochloride, hydrobromide or hydrogen sulfate.

9. A process for the preparation of 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile or its salt comprising the steps of, reacting a 2-butyl-1,3-diazaspiro[4.4]nonan-4-one hydrochloride with a 4'-(bromomethyl)[1,1'-biphenyl]-2-carbonitrile in a water-immiscible organic solvent, in the presence of an inorganic base and a phase transfer catalyst, separating the organic solvent, optionally drying the organic solvent, filtering the organic solvent, evaporating the filtered organic solvent to give an oily product, crystallizing the oily product from an organic solvent to give 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile and optionally converting it into its salt.

15

10. The process of claim 9, wherein the salt is a hydrochloride, hydrogen bromide or hydrogen sulfate.

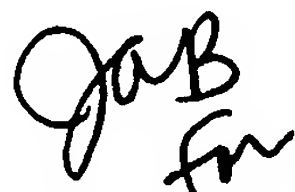
11. A process for the preparation of 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one or its salt, comprising the steps of, reacting a 2-butyl-1,3-diazaspiro[4.4]nonan-4-one hydrochloride with a 4'-(bromomethyl)[1,1'-biphenyl]-2-carbonitrile in a water-immiscible organic solvent, in the presence of an inorganic base and a phase transfer catalyst, separating the organic solvent, optionally drying the organic solvent, filtering the organic solvent, evaporating the filtered organic solvent to give an oily product, crystallizing the oily product from an organic solvent to give 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile, converting 4'-[[2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-carbonitrile to 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one and optionally converting into its salt.



12. The process of claim 11, wherein the salt is a hydrochloride, hydrogen bromide or hydrogen sulfate.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/01201

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) : C07D 233/30, 233/32, 233/36, 233/70, 235/00, 235/02 US CL : 548/324.5, 300.7 According to International Patent Classification (IPC) or to both national classification and IPC														
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 548/324.5, 300.7  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Please See Extra Sheet.  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)														
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>														
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
Y	US 5,126,342 A (CHAKRAVARTY et al.) 30 June 1992, see entire document.	1-12												
Y	US 5,268,375 A (BERNHART et al.) 07 December 1993, see entire document.	1-12												
Y	US 5,270,317 A (BERNHART et al.) 14 December 1993, see entire document.	1-12												
Y	US 5,424,450 A (BOSWELL et al.) 13 June 1995, see entire document.	1-12												
Y	US 5,434,167 A (FERRARI et al.) 18 July 1995, see entire document.	1-12												
Y	US 5,612,363 A (MOHAN et al.) 18 March 1997, see entire document.	1-12												
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.														
<table border="0"><tr><td>* Special categories of cited documents:</td><td>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td></tr><tr><td>*A* document defining the general state of the art which is not considered to be of particular relevance</td><td>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td></tr><tr><td>*B* earlier document published on or after the international filing date</td><td>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td></tr><tr><td>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td><td>*A* document member of the same patent family</td></tr><tr><td>*O* document referring to an oral disclosure, use, exhibition or other means</td><td></td></tr><tr><td>*P* document published prior to the international filing date but later than the priority date claimed</td><td></td></tr></table>			* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family	*O* document referring to an oral disclosure, use, exhibition or other means		*P* document published prior to the international filing date but later than the priority date claimed	
* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention													
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone													
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art													
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family													
*O* document referring to an oral disclosure, use, exhibition or other means														
*P* document published prior to the international filing date but later than the priority date claimed														
Date of the actual completion of the international search 22 MARCH 1999		Date of mailing of the international search report 01 APR 1999												
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer FLOYD D. HIGEL aco Telephone No. (703) 308-1235 												

Form PCT/ISA/210 (second sheet)(July 1992)\*

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/01201

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PEDREGAL ET AL. Etude de quelques derives N-3-substitues et N-1, N-3-disubstitues de la cyclohexano spirohydantione. J. Heterocyclic Chem., Mar-Apr 1984, Vol. 21, pages 477-480, see entire document.	1-12

Form PCT/ISA/210 (continuation of second sheet)(July 1992)★

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/01201

## B. FIELDS SEARCHED

Documentation other than minimum documentation that are included in the fields searched:

Chemical Abstracts

Current Abstracts of Chemistry

Index Chemicus